

Antibody Mediated Rejection as a Major Cause of Graft Dysfunction

Tapas Ranjan Behera¹, Biswaranjan Mohanty^{1*}, Sahu Alisha², Sujata Nayak³, Jatindra Nath Mohanty⁴

¹Associate Professor, Dept. Of Nephrology, IMS and SUM hospital, IMS and SUM hospital, SOA deemed to be University, Bhubaneswar- 751003, Odisha, India

²Senior resident, department of anaesthesia, IMS and SUM hospital, IMS and SUM hospital, SOA deemed to be University, Bhubaneswar- 751003, Odisha, India

³Associate Professor, Dept. Of Pathology, IMS and SUM hospital, IMS and SUM hospital, SOA deemed to be University, Bhubaneswar- 751003, Odisha, India

⁴Medical Research laboratory, IMS and SUM hospital, IMS and SUM hospital, SOA deemed to be University, Bhubaneswar- 751003, Odisha, India

Corresponding author

Dr. Biswaranjan Mohanty, Associate professor, Dept. Of Nephrology, IMS and SUM hospital, SOA deemed to be University, Bhubaneswar- 751003, Odisha, India

Mail Id- bishwaranjanmohanty@soa.ac.in

Abstract

Kidney transplantation is the best therapy available for most patients with ESRD. Antibody Mediated Rejection (AMR) in kidney transplantation is a severe complication that frequently occurs after transplantation. We retrospectively analysed histopathological reports of all patients (23 biopsies in 20 patients) who underwent kidney allograft biopsies for clinical indication, with the goal of understanding the pathology of graft dysfunction. In the early period of 0-6 weeks, 7(77.8%) cases had AMR and 2(22.2%) cases had acute tubular necrosis. In the period of 6 weeks- 6 months, 2(18.2%) cases had AMR, 7(63.6%) cases had mixed T+B cell mediated rejection and 2(18.2%) had features of BK virus nephropathy. In the 6-12 month period, only 1(100%) case had mixed T+B cell mediated rejection. After >12 months, 1(50%) had AMR and another one(50%) had mixed T+B cell mediated rejection. Out of all cases, 10(43.5%) had features of AMR, 9(39.1%) had mixed T+B cell mediated rejection, 2(8.7%) had BK virus nephropathy and another 2(8.7%) had features of ATN. In our study, we found the major cause of graft dysfunction is antibody-mediated rejection. Improvements in long-term renal allograft survival will require new and varied approaches specific for each pathogenic process.

Key words : AMR, Antibody Mediated Rejection, BK virus nephropathy, graft dysfunction

Introduction

Kidney transplantation is the best therapy available for most patients with end-stage kidney disease. Recent improvements in renal allograft survival relate primarily to a reduction in the incidence and consequences of T-cell mediated rejection. However, despite improvements in the outcomes of renal transplantation, the kidney allograft loss rate remains substantially high and is associated with increased mortality [1,2].

At present, insufficient control of the humoral arm of a recipient's immune system by the current immunosuppressive regimens [3] is the factor primarily responsible for allograft dysfunction and loss [4-6]. Calcineurin inhibitor toxicity contributes to injury and scarring in transplants (7) and native kidneys (8), but its actual contribution to late kidney graft failure is unknown. Recurrent diseases such as glomerulonephritis account for a minority of graft losses (9,10).

The recent demonstration that circulating donor-specific antibodies (DSA) against HLA antigens increase the risk of late graft loss (11) argues for a major role of antibody-mediated rejection (AMR). AMR was originally recognized by the presence of DSA and microcirculation injury (12), including electron microscopic changes (13), but is currently defined by deposition of complement factor C4d in peritubular capillaries (14–18). However, C4d may not be sensitive: many cases of transplant glomerulopathy with anti-HLA are C4d negative (19–21). Therefore, the recent update of the Banff classification introduced the diagnostic category 'suspicious for ABMR' if C4d (in the presence of antibody) or alloantibody (in the presence of C4d) cannot be demonstrated but morphologic evidence of antibody-mediated tissue injury is present (22). So our aim here is to analyze biopsies of kidney allografts for identifying causes of allograft dysfunction.

Materials and methods

Study population

All patients who underwent graft biopsies for graft dysfunction between July, 2012 and July, 2015 were included. Specimens were obtained under ultrasound guidance by Bard's kidney biopsy gun. All patients were recruited from the renal transplant unit, SCB Medical college.

The histological diagnostic criteria used were those proposed by the Banff group (23,24,25). Polyoma virus-associated nephropathy (PVAN) was diagnosed by the presence of BK virus in tubular epithelial cells by in situ hybridization. Glomerular diseases were diagnosed by light microscopy, immunofluorescence study. C4d staining was performed on frozen sections by indirect immunofluorescent staining using a monoclonal anti-C4d antibody.

All data were collected and pathology underlying graft dysfunction were analysed.

RESULTS

Patient demographics

We retrospectively studied all patients who underwent kidney allograft biopsies for clinical indication (n=23 biopsies in 20 patients {18 male and 2 female}) during the study period, with no selection. Patients were biopsied from 5 days to 2 years post-transplant.

Table 1 : Demographics data

Recipient Characteristics	Value
Recipient age (years, mean $\pm$ SD)	48.7 $\pm$ 17
Recipient sex (% males)	90 %
First transplant	100 %

Table 2: Donor details

Donor Characteristics	Value
Donor type (% living donor)	100 %
Donor sex (% males)	34.7 %
Donor age (years, mean $\pm$ SD)	42 $\pm$ 14

Mean recipient age was 48.7 years, with 90% were males. All biopsies were from first transplant cases. All(100%) grafts were from living donors. Male donors constitute 34.7% and females constitute 65.3%. Average age of donors was 42 years.

Table 3 : Histological Findings

DURATION					
Histological diagnosis	0-6 weeks	6weeks-6months	6-12months	>12 months	Total
Antibody mediated rejection	7(77.8%)	2(18.2%)	0	1(50%)	10(43.5%)
Mixed rejection	0	7(63.6%)	1(100%)	1(50%)	9(39.1%)
T cell mediated rejection	0	0	0	0	
BK virus nephropathy	0	2(18.2%)	0	0	2(8.7%)
ATN	2(22.2%)	0	0	0	2(8.7%)
Total	9(100%)	11(100%)	1(100%)	2(100%)	23

CNI toxicity was associated in 9 cases.

In the early period of 0-6 weeks, 7(77.8%) cases had AMR and 2(22.2%) cases had acute tubular necrosis. In the period of 6 weeks- 6 months, 2(18.2%) cases had AMR, 7(63.6%) cases had mixed T+B cell mediated rejection and 2(18.2%) had features of BK virus nephropathy. In the 6-12 month period, only 1(100%) case had mixed T+B cell mediated rejection. After >12 months, 1(50%) had AMR and another one(50%) had mixed T+B cell mediated rejection.

Out of all cases, 10(43.5%) had features of AMR, 9(39.1%) had mixed T+B cell mediated rejection, 2(8.7%) had BK virus nephropathy and another 2(8.7%) had features of ATN.

CNI toxicity was associated in 9 cases, out of which 5 cases were associated with AMR, 3 cases were associated with mixed T+B cell mediated rejection and 1 associated with ATN. Mean blood tacrolimus level in these cases was 12.7 ng/ml.

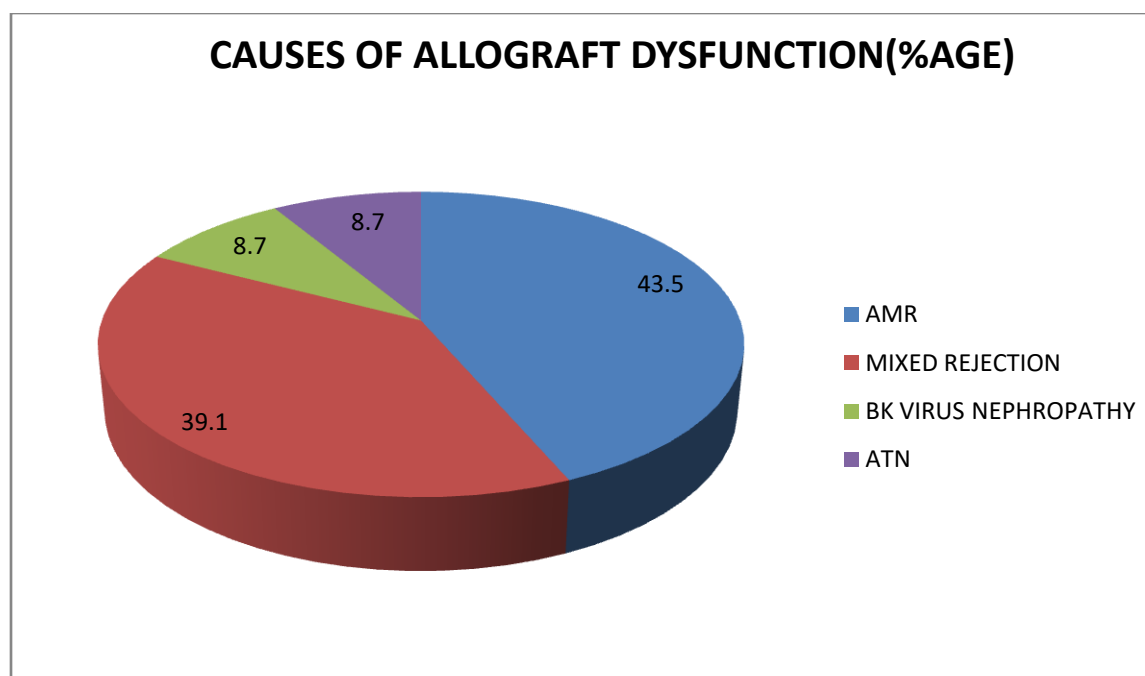


Figure 1: Causes of allograft dysfunction(%age)

DISCUSSION

We analyzed all biopsy findings with the goal of understanding the pathology of graft dysfunction. The majority of kidney failures were attributed to AMR, and mixed rejection. There was evidence of AMR in 10 out of 23 grafts which developed dysfunction and 9 out of 23 grafts showed evidence of mixed B+T cell rejection.

A prospective study by Sellarés J et al(5) indicates that many actual dysfunctions after indication biopsies manifest phenotypic features of antibody-mediated or mixed rejection.

The time of presenting with indications for biopsy and the original renal disease of the recipient are crucial in understanding the differential diagnoses and the risks of progression. In our study, AMR is the dominant cause in the early 0-6 weeks period and ATN also being found commonly in the same period, mixed rejection in the 6 week- 6 month period with findings of BK virus nephropathy also common in the same period.

In the 6-12 month period, only 1(100%) case had mixed T+B cell mediated rejection. After >12 months, 1(50%) had AMR and another one(50%) had mixed T+B cell mediated rejection.

Although calcineurin inhibitors are undoubtedly nephrotoxic and induce hyalinosis and fibrosis (26), this seldom progresses to end-stage disease in well-managed kidney transplants because effective options to limit progressive damage are available (27,28). However, it remains possible that calcineurin inhibitors play a role as accelerators of progressive diseases such as ABMR or GN, and this should be addressed in new studies. In our study, CNI toxicity was associated in 9 cases, out of which 5 cases were associated with AMR, 3 cases were associated

with mixed T+B cell mediated rejection and 1 associated with ATN. the mean tacrolimus level in these cases was 12.7 ng/ml.

Conclusion

This cohort indicates that many graft dysfunctions manifest phenotypic features of antibody-mediated or mixed rejection. AMR may occur early or even late after the transplantation. The indication-biopsy-based studies are probably the best available for estimating the main drivers of dysfunctions across the renal transplant population because they capture the full richness of the phenotype data. We conclude that improvements in long-term renal allograft survival will require new and varied approaches specific for each pathogenic process.

References

1. L'Agence de la biomédecine. Agence de la Biomédecine Annual Report[online] (2011)
2. Organ Procurement and Transplantation Network [online] (2012).
3. Salvadori M, Bertoni E (2013) Is it time to give up with calcineurin inhibitors in kidney transplantation? *World J Transplant* 3: 7-25.
4. Einecke G, Sis B, Reeve J, Mengel M, Campbell PM, et al. (2009) Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. *Am J Transplant* 9: 2520-2531.
5. Sellarés J, de Freitas DG, Mengel M, Reeve J, Einecke G, et al. (2012) Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant* 12: 388-399.
6. Gaston RS, Cecka JM, Kasiske BL, Fieberg AM, Leduc R, et al. (2010) Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. *Transplantation* 90: 68-74.
7. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; 349: 2326–2333.
8. Ojo AO, Held PJ, Port FK et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; 349: 931–940.
9. El Zoghby ZM, Stegall MD, Lager DJ et al. Identifying specific causes of kidney allograft loss. *Am J Transplant*. In press.
10. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002; 347: 103–109.
11. Mao Q, Terasaki PI, Cai J et al. Extremely high association between appearance of HLA antibodies and failure of kidney grafts in a five-year longitudinal study. *Am J Transplant* 2007; 7: 864–871.
12. Halloran PF, Wadgymar A, Ritchie S, Falk J, Solez K, Srinivasa NS. The significance of the anti-class I antibody response. I. Clinical and pathologic features of anti-class I-mediated rejection. *Transplant* 1990; 49: 85–91.

13. Racusen LC, Halloran PF, Solez K. Banff 2003 meeting report: New diagnostic insights and standards. *Am J Transplant* 2004; 4: 1562–1566.
14. Mauiyyedi S, Pelle PD, Saidman S et al. Chronic humoral rejection: Identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. *J Am SocNephrol* 2001; 12: 574–582.
15. Regele H, Bohmig GA, Habicht A et al. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: A contribution of humoral immunity to chronic allograft rejection. *J Am SocNephrol* 2002; 13: 2371–2380.
16. Mroz A, Durlik M, Cieciora T, Lao M. Complement split product C4 as the indicator of immunological activity in chronic allograft rejection. *Pol Merkur Lekarski* 2003; 15:363–365.
17. Vongwiwatana A, Gourishankar S, Campbell PM, Solez K, Halloran PF. Peritubular capillary changes and C4d deposits are associated with transplant glomerulopathy but not IgA nephropathy. *Am J Transplant* 2004; 4: 124–129.
18. Sijpkens YW, Joosten SA, Wong MC et al. Immunologic risk factors and glomerular C4d deposits in chronic transplant glomerulopathy. *Kidney Int* 2004; 65: 2409–2418.
19. Sis B, Campbell PM, Mueller T et al. Transplant glomerulopathy, late antibody-mediated rejection and the ABCD tetrad in kidney allograft biopsies for cause. *Am J Transplant* 2007; 7: 1743–1752.
20. Gloor JM, Sethi S, Stegall MD et al. Transplant glomerulopathy: Subclinical incidence and association with alloantibody. *Am J Transplant* 2007; 7: 2124–2132.
21. Miura M, Ogawa Y, Kubota KC et al. Donor-specific antibody in chronic rejection is associated with glomerulopathy, thickening of peritubular capillary basement membrane, but not C4d deposition. *Clin Transplant* 2007; 21: 8–12.
22. Solez K, Colvin RB, Racusen LC et al. Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant* 2008; 8: 753–760
23. Solez K, Axelsen RA, Benediktsson H et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int* 1993; 44: 411–422.
24. Solez K, Colvin RB, Racusen LC et al. Banff '05 Meeting Report: Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant* 2007; 7: 518–526.
25. Racusen LC, Colvin RB, Solez K et al. Antibody-mediated rejection criteria—an addition to the Banff 97 classification of renal allograft rejection. *Am J Transplant* 2003; 3: 708–714.
26. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; 349: 2326–2333.
27. ElZoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009; 9: 527– 535.
28. Sellares J, de Freitas DG, Mengel M, et al. Inflammation lesions in kidney transplant biopsies: Association with survival is due to the underlying diseases. *Am J Transplant* 2011; 11: 489–499.